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DOCUMENT-IDENTIFIER: US 20050196414 A1
TITLE: Compositions and methods for topical application and transdermal delivery of botulinum toxins

Abstract Paragraph:
A composition for topical application of a botulinum toxin (including botulinum toxin derivatives) comprises a botulinum toxin and a carrier comprising a polymeric backbone comprising a long-chain polypeptide or nonpeptidyl polymer having attached positively charged branching or "efficiency" groups. The invention also relates to methods for reducing muscle paralysis and other conditions that may be treated with a botulinum toxin, particularly paralysis of subcutaneous, and most particularly, facial, muscles, by topically applying an effective amount of the botulinum toxin and carrier, in conjunction, to the subject's skin or epithelium. Kits for administration are also described.

Summary of Invention Paragraph:
[0002] Skin protects the body's organs from external environmental threats and acts as a thermostat to maintain body temperature. It consists of several different layers, each with specialized functions. The major layers include the epidermis, the dermis and the hypodermis. The epidermis is a stratifying layer of epithelial cells that overlies the dermis, which consists of connective tissue. Both the epidermis and the dermis are further supported by the hypodermis, an internal layer of adipose tissue.

Summary of Invention Paragraph:
[0003] The epidermis, the topmost layer of skin, is only 0.1 to 1.5 millimeters thick (Inlander, Skin, New York, N.Y.: People's Medical Society, 1-7 (1998)). It consists of keratinocytes and is divided into several layers based on their state of differentiation. The epidermis can be further classified into the stratum corneum and the viable epidermis, which consists of the granular melphigian and basal cells. The stratum corneum is hygroscopic and requires at least 10% moisture by weight to maintain its flexibility and softness. The hygroscopicity is attributable in part to the water-holding capacity of keratin. When the horny layer loses its softness and flexibility it becomes rough and brittle, resulting in dry skin.

Summary of Invention Paragraph:
[0004] The dermis, which lies just beneath the epidermis, is 1.5 to 4 millimeters thick. It is the thickest of the three layers of the skin. In addition, the dermis is also home to most of the skin's structures, including sweat and oil glands (which secrete substances through openings in the skin called pores, or comedos), hair follicles, nerve endings, and blood and lymph vessels (Inlander, Skin, New York, N.Y.: People's Medical Society, 1-7 (1998)). However, the main components of the dermis are collagen and elastin.

Summary of Invention Paragraph:
[0005] The hypodermis is the deepest layer of the skin. It acts both as an insulator for body heat conservation and as a shock absorber for organ protection (Inlander, Skin, New York, N.Y.: People's Medical Society, 1-7 (1998)). In

addition, the hypodermis also stores fat for energy reserves. The pH of skin is normally between 5 and 6. This acidity is due to the presence of amphoteric amino acids, lactic acid, and fatty acids from the secretions of the sebaceous glands. The term "acid mantle" refers to the presence of the water-soluble substances on most regions of the skin. The buffering capacity of the skin is due in part to these secretions stored in the skin's horny layer.

Summary of Invention Paragraph:
[0006] Wrinkles, one of the telltale signs of aging, can be caused by biochemical, histological, and physiologic changes that accumulate from environmental damage (Benedetto, International Journal of Dermatology, 38:641-655 (1999)). In addition, there are other secondary factors that can cause characteristic folds, furrows, and creases of facial wrinkles (Stegman et al., The Skin of the Aging Face Cosmetic Dermatological Surgery, 2.sup.nd ed., St. Louis, Mo.: Mosby Year Book: 5-15 (1990)). These secondary factors include the constant pull of gravity, frequent and constant positional pressure on the skin (i.e., during sleep), and repeated facial movements caused by the contraction of facial muscles (Stegman et al., The Skin of the Aging Face Cosmetic Dermatological Surgery, 2.sup.nd ed., St. Louis, Mo.: Mosby Year Book: 5-15 (1990)). Different techniques have been utilized in order potentially to mollify some of the signs of aging. These techniques range from facial moisturizers containing alpha hydroxy acids and retinol to surgical procedures and injections of neurotoxins.

Summary of Invention Paragraph:
[0007] One of the principal functions of skin is to provide a barrier to the transportation of water and substances potentially harmful to normal homeostasis. The body would rapidly dehydrate without a tough, semi-permeable skin. The skin helps to prevent the entry of harmful substances into the body. Although most substances cannot penetrate the barrier, a number of strategies have been developed to selectively increase the permeability of skin with variable success.

Summary of Invention Paragraph:
[0010] The different serotypes of botulinum toxin vary in the animal species that they affect and in the severity and duration of the paralysis they evoke. For example, it has been determined that botulinum toxin type A is 500 times more potent, as measured by the rate of paralysis produced in the rat, than is botulinum toxin type B. Additionally, botulinum toxin type B has been determined to be non-toxic in primates at a dose of 480 U/kg, about 12 times the primate LD.sub.50 for type A. Due to the molecule size and molecular structure of botulinum toxin, it cannot cross stratum corneum and the multiple layers of the underlying skin architecture.

Summary of Invention Paragraph:
[0011] Botulism, the characteristic symptom complex from systemic botulinum toxin exposure, has existed in Europe since antiquity. In 1895, Emile P. van Ermengem first isolated the anaerobic spore-forming bacillus from raw salted pork meat obtained from post-mortem tissue of victims who died of botulism in Belgium. Van Ermengem found the disease to be caused by an extracellular toxin that was produced by what he called Bacillus botulinus (Van Ermengem, Z Hyyg Infektionskr, 26:1-56; Rev Infect (1897)). The name was changed in 1922 to Clostridium botulinum. The name Clostridium was used to reflect the anaerobic nature of the microorganism and also its morphologic characteristics (Carruthers and Carruthers, Can J Ophthalmol, 31:389-400 (1996)). In the 1920's, a crude form of Botulinum toxin type A was isolated after additional outbreaks of food poisoning. Dr. Herman Sommer at the University of California, San Francisco made the first attempts to purify the neurotoxin (Borodic et al., Ophthalmic Plast Recostr Surg, 7:54-60 (1991)). In 1946, Dr. Edward J. Schantz and his colleagues isolated the neurotoxin in crystalline form (Schantz et al., In: Jankovi J, Hallet M (Eds) Therapy with Botulinum Toxin, New York, N.Y.: Marcel Dekker, 41-49 (1994)). By 1949, Burgen and his associates were able to demonstrate that the Botulinum toxin blocks impulses

across the neuromuscular junction (Burgen et al., J Physiol, 109:10-24 (1949)). Allan B. Scott first used botulinum toxin A (BTX-A) in monkeys in 1973. Scott demonstrated reversible ocular muscle paralysis lasting 3 months (Lamanna, Science, 130:763-772 (1959)). Soon afterwards, BTX-A was reported to be a successful treatment in humans for strabismus, blepharospasm, and spasmodic torticollis (Baron et al., In: Baron E J, Peterson L R, Finegold S M (Eds), Bailey & Scotts Diagnostic Microbiology, St. Louis, Mo.: Mosby Year Book, 504-523 (1994); Carruthers and Carruthers, Adv Dermatol, 12:325-348 (1997); Markowitz, In: Strickland G T (Eds) Hunters Tropical Medicine, 7.sup.th ed. Philadelphia: W. B. Saunders, 441-444 (1991)). In 1986, Jean and Alastair Carruthers, a husband and wife team consisting of an ocuplastic surgeon and a dermatologist, began to evolve the cosmetic use of BTX-A for treatment of movement-associated wrinkles in the glabella area (Schantz and Scott, In Lewis G E (Ed) Biomedical Aspects of Botulinum, New York: Academic Press, 143-150 (1981)). The Carruthers' use of BTX-A for the treatment of wrinkles led to their seminal publication of this approach in 1992 (Schantz and Scott, In Lewis G E (Ed) Biomedical Aspects of Botulinum, New York: Academic Press, 143-150 (1981)). By 1994, the same team reported experiences with other movement-associated wrinkles on the face (Scott, Ophthalmol, 87:1044-1049 (1980)). This in turn led to the birth of the era of cosmetic BTX-A treatment.

Summary of Invention Paragraph:
[0014] This invention relates to new compositions comprising a botulinum toxin, more specifically to such compositions that enable the transport or delivery of a botulinum toxin through the skin or epithelium (also referred to as "transdermal delivery"), and that therefore may be used as topical applications for providing a botulinum toxin to a subject, for various therapeutic, aesthetic and/or cosmetic purposes, as described herein.

Summary of Invention Paragraph:
[0017] Yet another aspect of this invention is to provide a kit for administration of a botulinum toxin to a subject. The kit includes a device for delivering the botulinum toxin to the skin and a composition containing a carrier having a polymeric backbone with attached positively charged branching groups selected from -(gly).sub.n1-(arg).sub.n2, HIV-TAT and fragments thereof, and Antennapedia PTD, in which the subscript n1 is an integer of from 0 to about 20, and the subscript n2 is independently an odd integer of from about 5 to about 25.

Summary of Invention Paragraph:
[0018] This invention also provides a method of administering a botulinum toxin to a subject involving topically applying to the skin or epithelium of the subject the botulinum toxin in conjunction with an effective amount of a carrier. The carrier has a polymeric backbone with attached positively charged branching groups, and associates non-covalently with the botulinum toxin.

Summary of Invention Paragraph:
[0019] In one aspect, this invention relates to a composition comprising a botulinum toxin (as defined herein) and a carrier comprising a positively charged "backbone" having positively charged branching or "efficiency" groups, as described herein. Most preferably the positively charged carrier is a long-chain positively charged polypeptide or a positively charged nonpeptidyl polymer, for example, a polyalkyleneimine. The invention further relates to a method for producing a biologic effect such as muscle paralysis, reducing hypersecretion or sweating, treating neurologic pain or migraine headache, reducing muscle spasms, preventing or reducing acne, or reducing or enhancing an immune response, by topically applying an effective amount of such a composition, preferably to the skin, of a subject or patient in need of such treatment. The invention also relates to a method for producing an aesthetic or cosmetic effect, for example by topical application of botulinum toxin to the face instead of by injection into facial muscles.

Brief Description of Drawings Paragraph:
[0027] FIG. 7 shows the dose area used in the axillary hyperhidrosis studies. Note that the dose area extends one centimeter beyond the area of the skin covered by axillary hair.

Brief Description of Drawings Paragraph:
[0028] FIG. 8a represents the results of an experiment demonstrating efficiency of botulinum toxin therapeutically delivered across intact skin as a topical agent using a short peptidyl carrier for the treatment of axillary hyperhidrosis on human subjects. Graph depicts significant reduction in amount of sweat (mg per 5 minutes) measured gravimetrically 4 weeks after treatment with Botox plus a short peptidyl carrier or carrier alone. Results are 4 week values as ratio to baseline value for same group, with significance determined by Wilcoxon analysis with $P<0.05$. N=10 patients.

Brief Description of Drawings Paragraph:
[0029] FIG. 8b represents the results of an experiment demonstrating efficiency of botulinum toxin therapeutically delivered across intact skin as a topical agent using a short peptidyl carrier for the treatment of axillary hyperhidrosis on human subjects. Graph depicts significant reduction in amount of sweat (mg per 5 minutes) measured gravimetrically 4 weeks after treatment with Botox plus a short peptidyl carrier or carrier alone. Results are treatment values as ratio to control value for both timepoints, with significance determined by Wilcoxon analysis with $P<0.05$. N=10 patients.

Detail Description Paragraph:
[0032] According to the present invention, a positively charged carrier molecule having efficiency groups, as described herein, has been found suitable as a transport system for a botulinum toxin, enabling that toxin to be administered transdermally to muscles and/or other skin-associated structures. The transport occurs without covalent modification of the botulinum toxin.

Detail Description Paragraph:
[0047] Compositions of this invention are preferably in the form of products to be applied to the skin or epithelium of subjects or patients, i.e. humans or other mammals in need of the particular treatment. The term "in need" is meant to include both pharmaceutical or health-related needs, for example, treating conditions involving undesirable facial muscle spasms, as well as cosmetic and subjective needs, for example, altering or improving the appearance of facial tissue. In general the compositions are prepared by mixing the botulinum toxin with the carrier, and usually with one or more additional pharmaceutically acceptable carriers or excipients. In their simplest form they may contain a simple aqueous pharmaceutically acceptable carrier or diluent, such as buffered saline. However, the compositions may contain other ingredients typical in topical pharmaceutical or cosmeceutical compositions, including a dermatologically or pharmaceutically acceptable carrier, vehicle or medium, (i.e. a carrier, vehicle or medium that is compatible with the tissues to which they will be applied.) The term "dermatologically or pharmaceutically acceptable," as used herein, means that the compositions or components thereof so described are suitable for use in contact with these tissues or for use in patients in general without undue toxicity, incompatibility, instability, allergic response, and the like. As appropriate, compositions of the invention may comprise any ingredient conventionally used in the fields under consideration, and particularly in cosmetics and dermatology. The compositions also may include a quantity of a small anion, preferably a polyvalent anion, for example, phosphate, aspartate, or citrate.

Detail Description Paragraph:
[0048] In terms of their form, compositions of this invention may include solutions, emulsions (including microemulsions), suspensions, creams, lotions, gels, powders, or other typical solid or liquid compositions used for application

to skin and other tissues where the compositions may be used. Such compositions may contain, in addition to the botulinum toxin and carrier, other ingredients typically used in such products, such as antimicrobials, moisturizers and hydration agents, penetration agents, preservatives, emulsifiers, natural or synthetic oils, solvents, surfactants, detergents, emollients, antioxidants, fragrances, fillers, thickeners, waxes, odor absorbers, dyestuffs, coloring agents, powders, and optionally including anesthetics, anti-itch additives, botanical extracts, conditioning agents, darkening or lightening agents, glitter, humectants, mica, minerals, polyphenols, silicones or derivatives thereof, sunblocks, vitamins, and phytomedicinals.

Detail Description Paragraph:
[0049] In particularly preferred embodiments, the compositions include gelling agents and/or viscosity-modifying agents. These agents are generally added to increase the viscosity of the composition, so as to make the application of the composition easier and more accurate. Additionally, these agents help to prevent the aqueous botulinum toxin/carrier solution from drying out, which tends to cause a decrease in the activity of the botulinum toxin. Particularly preferred agents are those that are uncharged and do not interfere with the botulinum toxin activity or the efficiency of the toxin-carrier complexes in crossing skin. The gelling agents may be certain cellulose-based gelling agents, such as hydroxypropylcellulose (HPC) for example. In some embodiments, the botulinum toxin/carrier complex is formulated in a composition having 2-4% HPC. Alternatively, the viscosity of a solution containing a botulinum toxin/carrier complex may be altered by adding polyethylene glycol (PEG). In other embodiments, the botulinum toxin/carrier solution is combined with pre-mixed viscous agents, such as Cetaphil.RTM. moisturizer.

Detail Description Paragraph:
[0053] Compositions according to this invention may be in the form of controlled-release or sustained-release compositions, wherein the botulinum toxin and the carrier are encapsulated or otherwise contained within a material such that they are released onto the skin in a controlled manner over time. The botulinum toxin and carrier may be contained within matrixes, liposomes, vesicles, microcapsules, microspheres and the like, or within a solid particulate material, all of which is selected and/or constructed to provide release of the botulinum toxin over time. The botulinum toxin and the carrier may be encapsulated together (e.g., in the same capsule) or separately (in separate capsules).

Detail Description Paragraph:
[0054] Using the compositions described herein, botulinum toxin can be delivered to muscles underlying the skin, or to glandular structures within the skin, in an effective amount to produce paralysis, produce relaxation, alleviate contractions, prevent or alleviate spasms, reduce glandular output, or other desired effects. Local delivery of the botulinum toxin in this manner could afford dosage reductions, reduce toxicity and allow more precise dosage optimization for desired effects relative to injectable or implantable materials.

Detail Description Paragraph:
[0055] The compositions of the invention are applied so as to administer an effective amount of the botulinum toxin. The term "effective amount" as used herein means an amount of a botulinum toxin as defined above that is sufficient to produce the desired muscular paralysis or other biological or aesthetic effect, but that implicitly is a safe amount, i.e. one that is low enough to avoid serious side effects. Desired effects include the relaxation of certain muscles with the aim of, for instance, decreasing the appearance of fine lines and/or wrinkles, especially in the face, or adjusting facial appearance in other ways such as widening the eyes, lifting the corners of the mouth, or smoothing lines that fan out from the upper lip, or the general relief of muscular tension. The last-mentioned effect, general relief of muscular tension, can be effected in the face or elsewhere. The

compositions of the invention may contain an appropriate effective amount of the botulinum toxin for application as a single-dose treatment, or may be more concentrated, either for dilution at the place of administration or for use in multiple applications. Through the use of the positively charged carriers of this invention, a botulinum toxin can be administered transdermally to a subject for treating conditions such as undesirable facial muscle or other muscular spasms, hyperhidosis, acne, or conditions elsewhere in the body in which relief of muscular ache or spasms is desired. The botulinum toxin is administered topically for transdermal delivery to muscles or to other skin-associated structures. The administration may be made, for example, to the legs, shoulders, back (including lower back), axilla, palms, feet, neck, groin, dorsa of the hands or feet, elbows, upper arms, knees, upper legs, buttocks, torso, pelvis, or any other part of the body where administration of the botulinum toxin is desired.

Detail Description Paragraph:
[0058] Most preferably, the compositions are administered by or under the direction of a physician or other health care professional. They may be administered in a single treatment or in a series of periodic treatments over time. For transdermal delivery of botulinum toxin for the purposes mentioned above, a composition as described above is applied topically to the skin at a location or locations where the effect is desired. In embodiments were an aqueous botulinum toxin/carrier solution is applied directly to the skin, it is preferable to cover the treated area (e.g., with Cetaphil.RTM. moisturizer) or occlude the treated area with a barrier (e.g., Telfa), in order to prevent the solution from drying out, which would lead to a decrease in toxin activity. Because of its nature, most preferably the amount of botulinum toxin applied should be applied with care, at an application rate and frequency of application that will produce the desired result without producing any adverse or undesired results. Accordingly, for instance, topical compositions of the invention should be applied at a rate of from about 1U to about 20,000U, preferably from about 1U to about 10,000U botulinum toxin per cm.sup.2 of skin surface. Higher dosages within these ranges could preferably be employed in conjunction with controlled release materials, for instance, or allowed a shorter dwell time on the skin prior to removal.

Detail Description Paragraph:
[0059] Proper preparation of the skin surface prior to the application of the botulinum toxin/carrier composition is important for maintaining the efficacy of the solution. For example, the introduction of surfactants on the surface of the skin for the purpose of cleaning off surface oils on the skin prior to application is surprisingly counterproductive, because the surfactants appear to destroy the activity of the botulinum toxin. This occurs even if the skin is subsequently washed with water several times before application of the botulinum toxin/carrier solution. Even extremely gentle surfactants, such as those found in baby wipes, appear to cause this phenomenon. Accordingly, in preferred methods of administering the compositions of this invention, the skin is pre-cleaned using water alone. Washing with only water also appears to improve the transdermal transport of the botulinum toxin moderately.

Detail Description Paragraph:
[0060] Additionally, the skin may be stripped to reduce the stratum corneum layer prior to application of the botulinum toxin/carrier complex. In principle, the process of stripping the skin should lead to enhanced efficiency of transdermal transport of botulinum toxin. However, the method used to strip the skin is important. For example, acetone-mediated reduction of the stratun corneum layer in humans or animals appears to reduce the activity of subsequently applied botulinum toxin. In contrast, tape stripping (i.e., applying tape on the surface of the skin and then removing the tape) appears to allow deeper penetation of the botulinum toxin and dosage reduction in both mouse models and humans. It is presumed that abrasion of the skin surface (e.g, via the use of abrasive pads) would cause a similar effect as tape stripping.

Detail Description Paragraph:
[0061] This invention also comprises devices for transdermal transmission of a composition that contains botulinum toxin and a carrier that has a positively charged backbone with attached branching groups as defined herein. Such devices may be as simple in construction as a skin patch, or may be more complicated devices that include means for dispensing and monitoring the dispensing of the composition, and optionally means for monitoring the condition of the subject (e.g., monitoring the reaction of the subject to the substances being dispensed).

Detail Description Paragraph:
[0064] In general, the invention also comprises a method for administering a botulinum toxin to a subject or patient in need thereof. The method includes comprising topically administering an effective amount of the botulinum toxin in conjunction with a carrier having a positively charged backbone with attached positively charged branching groups, as described herein. By "in conjunction with" is meant that the two components (botulinum toxin and carrier) are administered in a combination procedure, which may involve either combining them in a composition, which is subsequently administered to the subject, or administering them separately, but in a manner such that they act together to provide the requisite delivery of an effective amount of the therapeutic protein. For example, a composition containing the carrier may first be applied to the skin of the subject, followed by applying a skin patch or other device containing the botulinum toxin. The botulinum toxin may be incorporated in dry form in a skin patch or other dispensing device, while the positively charged carrier may be applied to the skin surface before application of the patch so that the two act together, resulting in the desired transdermal delivery. Thus, the two substances (carrier and botulinum toxin) act in combination or perhaps interact to form a composition or combination in situ. Accordingly, the invention also comprises a kit that includes both a device for dispensing botulinum toxin via the skin and a liquid, gel, cream or the like that contains the carrier or backbone, and that is suitable for applying to the skin or epithelium of a subject. Kits for administering the compositions of the inventions, either under direction of a health care professional or by the patient or subject, may also include a custom applicator suitable for that purpose.

Detail Description Paragraph:
[0066] The following are representative examples of the invention. They demonstrate delivery of functional botulinum neurotoxin complexes across skin without requiring covalent modification of the neurotoxin to be delivered.

Detail Description Paragraph:
[0067] This experiment demonstrates the use of a peptidyl carrier to transport a large complex containing an intact labeled protein botulinum toxin across intact skin after a single time administration relative to controls.

Detail Description Paragraph:
[0078] Animals were anesthetized via inhalation of isoflurane during application of treatments. After being anesthetized, C57 black 6 mice (n=4 per group) underwent topical application of a metered 200 microliter dose of the appropriate treatment applied to the cranial portion of dorsal back skin (selected because the mouse cannot reach this region with mouth or limbs). Animals did not undergo depilation. At 30 minutes after the initial treatment, mice were euthanized via inhalation of CO.sub.2, and treated skin segments were harvested at full thickness by blinded observers. Treated segments were divided into three equal portions; the cranial portion was fixed in 10% neutral buffered formalin for 12-16 hours then stored in 70% ethanol until paraffin embedding. The central portion was snap-frozen and employed directly for biotin visualization by blinded observers as summarized below. The treated caudal segment was snap frozen for solubilization studies.

Detail Description Paragraph:

[0084] Example 1 demonstrated that the peptidyl transdermal carrier allowed efficient transfer of botulinum toxin after topical administration in a murine model of intact skin. However, this experiment did not indicate whether the complex protein botulinum toxin was released in a functional form after translocation across skin. The following experiment was thus constructed to evaluate whether botulinum toxin can be therapeutically delivered across intact skin as a topical agent using this peptidyl carrier (again, without covalent modification of the protein).

Detail Description Paragraph:
[0094] Mean digital abduction scores after single-time topical administration of botulinum toxin with KNR ("JMW-9"), K ("JMW-10") or diluent without polycation ("JMW-11"), are presented in table 2 and illustrated in the representative photomicrograph of FIG. 2 below. The peptidyl carrier KNR afforded statistically significant functional delivery of the botulinum toxin across skin relative to both controls, which were comparable to one another. Additional independent repetitions (total of three independent experiments all with identical conclusions in statistically significant paralysis from topical botulinum toxin with KNR but not controls) of the present experiment confirmed the present findings and revealed no significant differences between topical botulinum toxin with or without K (i.e. both controls). Interestingly, the mice consistently ambulated toward a paralyzed limb (which occurred in 100% of treated animals and 0% of controls from either control group). As shown in FIG. 2, a limb treated with botulinum toxin plus the control polycation polylysine or with botulinum toxin without polycation ("Botox alone") can mobilize digits (as a defense mechanism when picked up), but the limbs treated with botulinum toxin plus the peptidyl carrier KNR ("Essentia Botox lotion") could not be moved.

Detail Description Paragraph:
[0096] This experiment serves to demonstrate that the peptidyl transdermal carrier can transport a therapeutically effective amount of botulinum therapeutic across skin without covalent modification of the therapeutic. The experiment also confirms that botulinum toxin does not function when applied topically in controls.

Detail Description Paragraph:
[0109] Mean digital abduction scores after single-time topical administration of botulinum toxin with ultrapure PEIR ("AZ"), or control polycation PEI ("BA"), are presented in table 3 and repetition presented as table 4 (single independent repetition for this experiment). The nonpeptidyl carrier PEIR afforded statistically significant functional delivery of botulinum toxin across skin relative to controls. As before, animals were observed to walk in circles toward the paralyzed limbs.

Detail Description Paragraph:
[0112] This experiment demonstrated that the nonpeptidyl transdermal carrier can transport therapeutic doses of botulinum toxin across skin without prior covalent modification of the botulinum toxin. These findings complement those with peptidyl transfer agents. The option of using a nonpeptidyl or a peptidyl carrier to achieve the therapeutic effect will allow tailoring to specific circumstances, environments, and methods of application and add to the breadth of the transdermal delivery platform of this invention.

Detail Description Paragraph:
[0113] This experiment demonstrates that botulinum toxin can be therapeutically delivered across intact skin as a topical agent using this peptidyl carrier for the treatment of forehead hyperhidrosis and wrinkles on human subjects.

Detail Description Paragraph:
[0123] The subject reclined on a table with protective covering around the eyes, face, and upper body. The treatment was applied evenly to the subject's forehead

using a pipette and massaged into the skin in circular motion with fingers while wearing powder-free, nitrile gloves. The treatment area was covered with a thin layer of Cetaphil.RTM. moisturizing cream (Galderma, Fort Worth, Tex.) and incubated for 60 minutes. After 60 minute incubation, the treatment was removed with sterile gauze pads. The gauze pads and gloves were discarded in a biohazard bag.

Detail Description Paragraph:
[0125] FIG. 3 depicts significant reduction in wrinkle length depth and width after topical treatment with Peptidyl carrier and botulinum combination. This experiment confirms that topically applied botulinum toxin, when combined with transdermal carrier, can afford significant muscular paralysis to afford a cosmetic effect. FIG. 4 is a Mikrosil cast of the treated skin (A) versus untreated skin (B). Wrinkles are visible on the cast of the untreated skin.

Detail Description Paragraph:
[0126] FIGS. 5 and 6 show the results of the Minor's starch/iodine test. FIG. 5 shows photos taken two minutes after application, with panel (A) corresponding to the side treated with Essentia Botox Lotion, and panel (B) corresponding to the side treated with a control lotion containing Kn21T carrier alone. FIG. 6 is the same as FIG. 5, except that it was taken at four minutes. Note the more pronounced coloration on the control lotion side, indicating that the skin on that side is secreting more sweat. Also note that the sweating starts earlier on the untreated side.

Detail Description Paragraph:
[0129] This experiment demonstrates whether botulinum toxin can be therapeutically delivered across intact skin as a topical agent using this peptidyl carrier for the treatment of axillary hyperhidrosis on human subjects (n=10 axillae per group with one axilla treated and one control per patient in a randomized double-blind fashion).

Detail Description Paragraph:
[0142] Axillae preparation: (Powder-free, nitrile gloves were worn for the following procedures.) The subject changed into disposable cape and bra (if a woman) or took off all upper body garments (if a man) so as to expose both of the axillae fully. The dose area was predetermined to be the area covered by hair bearing skin, plus an area extending 1 cm beyond the hair bearing skin at each axilla. The dose area was cleaned with a pre-wet sterile gauze pad from a 50 ml conical tube by wiping with 5 long strokes from top to bottom in the same direction using one side of the gauze. This step was repeated three more times with a clean pre-wet gauze pad each time while being careful not to irritate or abrade the skin. The gauze pads were discarded in the trash. The same wash procedure was repeated for the other axilla. The axilla was dried with dry sterile gauze by using firm padding motion from top to bottom of the axilla while being careful not to irritate or abrade the skin. Then, the axilla was further dried by placing a filter paper under the axillary crease and allowing the filter to dwell in the test site for 5 minutes following the procedure for gravimetric assessment. The patient sat with their arms against his/her body in a resting position. The filter papers were discarded in the trash. The subject was allowed to rest for 1 minute without axilla manipulation prior to the first gravimetric assessment.

Detail Description Paragraph:
[0150] The subject held his/her hands together with interlocking fingers and placed them on the back of the head to fully exposure the subject's axillae. Then, the subject reclined in a chair to an angle of about 45 degrees. As shown in FIG. 7, the dose area was visually mapped out (i.e. 1 cm beyond the hair bearing skin) for application. The dose area were checked for dryness. The syringe tip cap was removed from the labeled syringe marked "L" for left and "R" for right, and prepared for application onto the subject's axilla. The treatment solution was

spread evenly around the dose area with a syringe and massaged into the skin with fingers for 1 minute. The subject then placed his/her arms down along the side of the body and incubated for 60 minutes. After 60 minute incubation, the treatment was cleaned with sterile gauze pads. The gauze pads and gloves were discarded in a bio-hazard bag. The subject was discharged.

CLAIMS:

47. A kit according to claim 41 in which the botulinum toxin is contained in a device for administering the botulinum toxin to a subject via the skin.

48. A kit according to claim 47 in which the device is a skin patch.

49. A kit for administration of a botulinum toxin to a subject comprising a device for delivering the botulinum toxin to the skin and a composition comprising a carrier comprising a polymeric backbone having attached positively charged branching groups selected from -(gly).sub.n1-(arg).sub- .n2, HIV-TAT and fragments thereof, and Antennapedia PTD, in which the subscript n1 is an integer of from 0 to about 20, and the subscript n2 is independently an odd integer of from about 5 to about 25.

50. A kit according to claim 49 in which the device is a skin patch.

51. A method of administering a botulinum toxin to a subject comprising topically applying to the skin or epithelium of the subject the botulinum toxin in conjunction with an effective amount of a carrier comprising a polymeric backbone having attached positively charged branching groups, wherein the association between the carrier and the botulinum toxin is non-covalent.

52. A method according to claim 51 comprising topically applying to the skin or epithelium of the subject an effective amount of a composition according to claim 1.

53. A method according to claim 51 in comprising separately applying the botulinum toxin and the carrier to the skin or epithelium of the subject.

116. A method according to claim 51 in which the botulinum toxin is contained in a device for dispensing the botulinum toxin, which device is applied topically to the skin or epithelium of the subject.

117. A method according to claim 116 in which the device is a skin patch.

126. A method according to claim 54 in which the botulinum toxin is applied topically for improvement of wound healing.

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